50. A therapeutic composition according to claim 48, wherein the therapeutic gene comprises a CyP2B6 gene.--

REMARKS

Claims 1-24 have been cancelled, without prejudice. Claims 25-50 have been added, to advance prosecution. Support for the amended claims is found throughout the specification. No new matter has been added.

The Section 112, first paragraph, rejection of claims 1-18 and 21-24 is moot in view of the above. The Examiner's consideration of the following, however, is respectfully requested as the applicants respectfully submit that claims 1-18 and 21-24 were sufficiently supported, and claims 25-50 are supported, by an enabling disclosure.

The applicants submit that originally filed claims 1-18 and 21-24 are sufficiently described. In this respect, the term "therapeutic composition" relates to a composition comprising a therapeutic agent/gene which can be used in *ex vivo* gene delivery or *in vivo* gene delivery. The therapeutic agent/gene may be a pro-drug activation enzyme (see, page 8, line 15) or a suicide gene (see, page 12, line 20). A list of suitable genes is provided on page 15, lines 1-25. Examples of ways of delivering the therapeutic gene are described on page 37, lines 11-24 and page 38, lines 1-20.

In view of the Examiner's comments regarding gene therapy, applicants submit that the present invention is sufficiently exemplified for methods of *in vivo* and *ex vivo* gene delivery/gene transfer. There is a basis for this statement on page 14, line 7, page 20, line 22.

delivery such as the preparation of a retroviral vector and its transfer to U937 monocytic cell lines (see, page 21, Example 1) and gene transfer to primary human macrophages using an adenoviral vector (Example 2).

The applicants submit that the purpose of Example 5 is to demonstrate the effect of clamp induced hypoxia on macrophage infiltration into tumor xenografts. The clamping of the tumors induces hypoxia in the tumors which led to increased infiltration of macrophages (see, page 33, lines 23-24). This result demonstrated a correlation between the degree of hypoxia and the number of infiltrating macrophages. This result strengthens the applicants' assertions that mononuclear phagocytes may be used to deliver drugs to hypoxic/ischaemic sites where mononuclear phagocytes are typically present (see, page 5, lines 22-25).

The pending claims are supported by an enabling disclosure such that one of ordinary skill would have been able to make and use the presently claimed invention without undue experimentation.

Similarly, the Section 112, first paragraph, rejection of claims 19 and 20, stated at ¶6 of the Office Action of July 7, 2000 (Paper No. 5) is moot in view of the above. The pending claims are submitted to be supported by an enabling disclosure and the Examiner is requested to consider the above with regard to the comments of ¶6.

The Section 112, second paragraph, rejection of claim 19 is moot in view of the above. The claims have been amended in view of the Examiner's comments and are submitted to be definite.

The Section 103 rejection of claims 1-22 over Ferkol (U.S. Patent No. 5,972,900) in view of Ratcliffe (U.S. Patent No. 5,942,434) and Leek (Cancer Research, Vol. 56, 15 October 1996,

be patentable over the Examiner combination of references and the Examiner is requested to consider the following in this regard.

Ferkol et al (1996) describe *in vitro* and *in vivo* gene transfer into macrophages using a non-viral system by specifically targeting the mannose receptor in macrophages.

Ferkol does not teach that a gene comprising a regulatable agent such as a hypoxia, ischemia or stress regulatable agent could be transferred into macrophages. In fact, the Ferkol (1996) disclosure points away from the present invention as it is stated on page 104, first paragraph that their method of gene transfer (linking DNA to a polycationic protein such a poly-L-lysine) would be unsuitable for circulating monocytes, which randomly migrate into various tissues as these monocytes have few mannose receptors.

Ratcliffe relates to nucleic acid constructs comprising at least one gene encoding a species having activity against disease, operatively linked to a hypoxically inducible expression control sequence. Ratcliffe does not disclose monouclear phagocytes comprising a hypoxic and/or ischaemic and/or stress regulatable agent for targeting a therapeutic gene to a tumor site.

Leek teaches that macrophage infiltration was strongly associated with reduced relapse-free interval and reduced overall survival in patients with breast cancer. Reference is made to this citation on page 3, lines 7-17 of the application as filed. Although Leek suggest that the areas of greatest macrophage density or "macrophage hot spots" imply active macrophage migration rather than accumulation, Leek states that:

"the factors that induce macrophage hot spots are not clear but may include necrosis and hypoxia"

In addition, while Leek suggests that:

Leek does not disclose or suggest that mononuclear phagocytes comprising a hypoxic and/or ischaemic and/or stress regulatable agent may be useful in targeting a therapeutic gene to a tumor site.

Accordingly, the ordinarily skilled person would not have combined the teachings of Ferkol, Ratcliffe and Leek as Ferkol points away from the presently claimed invention and neither Ratcliffe nor Leek disclose or suggest that mononuclear phagocytes comprising a hypoxic and/or ischaemic and/or stress regulatable agent may be useful in targeting a therapeutic gene to a tumor site.

In view of the above, the pending claims are submitted to be patentable over the Examiner's combination of cited art.

The claims are submitted to be in condition for allowance and Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

B.J. Sadoff
Reg. No. 36,663

BJS:rdw
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4091
Facsimile: (703) 816-4100